REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on January 5, 2004, and the document cited therewith.

Objection to the Specification

The Examiner has objected to the brief description of the drawings provided at page 7 of the specification as incomplete insofar as a description of Figures 8A, 8B, 8C and 8D (each is its own individual figure) is not provided. The amendment provided herein is believed to provide the description required. It is respectfully requested that this objection be withdrawn.

§103 Rejection of the Claims

Claims 1, 3-4, 11, 13-14, 26-29, and 34-35 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Loma Linda University Medical Center WO 98/09603 A2 ("the '603 application"). The Examiner has alleged that the claimed use of etodolac would be obvious in view of the '603 application. This rejection is respectfully traversed.

The present claims are directed to the use of a group pyranylindanoacetic acids, including the non-steroidal anti-inflammatory agent (NSAID) etodolac, to reduce the viability of cancerous bone marrow cells. The claims are based on the unexpected discovery that etodolac has the ability to kill the type of cancerous cells that characterize myelomas.

The Examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the Examiner does not establish a prima facie case, the applicant is under no obligation to submit evidence of non-obviousness. M.P.E.P. §2142. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. M.P.E.P. §2142.

The claimed invention is a method for "treating multiple myeloma" by contacting the cells with an effective amount of etodolac or an analog thereof. The invention, is different from the '603 application disclosure, which discloses a method to prevent the onset or formation of

colorectal cancer with R-NSAIDs. This is important in colon cancer due to the manifestation of pre-cancerous proliferating cells prior to the onset of cancer. See page 1, lines 17-35. There is no suggestion in the '603 application that etodolac or its analogs would be useful for treating established diseases by killing active cancer cells. In fact, conventional chemotherapeutic treatments for colon cancer for use after cancer has been diagnosed, are disclosed at page 2, line 33 to page 3, line 13.

The '603 application, after disclosing the "treatment" of neoplastic disease (page 7, line 17) in fact defines treatment as a chemoprotective effect, and discloses several tests to measure the prevention of formation of cancerous cells. (See page 7, line 31 to page 8, line 13.) In fact, the claims (See claim 24) of the application recite "eliciting a chemoprotective effect." The essence of the invention disclosed in the '603 application is a method to prevent the formation of cancerous neoplasms or tumors by inhibition of proliferation and not to reduce the viability or sensitize cancer cells. Finally, at page 11, line 26, the '603 application uses the terms prophylactic and therapeutic in the alternative. This use, along with the remainder of the disclosure, supports the conclusion that the '603 application discloses only a method for prevention of the formation of cancer and does not disclose or suggest that the compounds are useful for killing or reducing the viability of cancer cells.

The M.P.E.P. § 2141.02 states that a "prior art" document must be considered as a whole, including those portions that teach away from the claimed invention. The '603 application discloses that R-NSAIDS provide a "chemoprotective effect" or a prophylactic effect, *i.e.*, the prevention of the occurrence of cancer. This use, to provide a "chemoprotective effect" or to prevent cancer, is repeated throughout the specification. (See, page 6, line 9; page 6, line 16; page 7, line 18; page 7, lines 31-32; page 8, lines 6-8; and page 9, lines 5-8.) In particular, at page 7, lines 31-32 (cited by the Examiner) states:

> The term "effective to elicit a chemoprotective effect" as used herein means that abnormal cell proliferation is reduced.

At page 9, lines 5-8 the '603 application defines the claimed "chemoprotective effect" as follows:

> The term "eliciting a colorectal chemoprotective effect" as used herein means relieving, ameliorating or preventing colorectal cancers. Specifically, it means that abnormal cell proliferation in the colon and rectum are reduced. (Emphasis added).

Thus, the '603 application is directed to "treating" colorectal cancer, or neoplastic disease, with a R-NSAID only so far as to elicit a chemoprotective effect, which is reduction of abnormal cell proliferation. The "chemoprotective effects" of the inhibition of the conversion of intestinal polyps to neoplastic or cancerous lesions or of preventing induction of tumors in carcinogen-treated animals, is not a suggestion to use R-NSAIDs to kill active cancer cells or to reduce their viability.

In the Office Action, the Examiner admits that the claims are not anticipated by the '603 application because "It does not teach treatment of multiple myeloma specifically with R-etodolac." (See page 4, line 1 of Office Action.) Further, the application does not disclose an embodiment or a working example of the use presently claimed. However, he asserts that it would be obvious for a person having ordinary skill in the art to select the specific cancer, multiple myeloma, and NSAID, R-etodolac, based on the disclosure and two separate lists therein. One list is a group of five potential cancers. This list, as admitted by the Examiner, is missing multiple myeloma. The other is a list of eleven NSAIDs that the '603 application indicates may be useful. Finally, Applicants note, that there is only one example that relates to prophylactic treatment using an NSAID. That example uses flurbiprofen. The other examples are directed to an example that assayed the toxicity of R-etodolac and inhibitory effect of cyclooxygenase activity using the NSAID ketoprofen.

The Examiner has admitted that there is no explicit teaching or suggestion of the instant claims, *i.e.*, that the specific compounds claimed will be effective for treating multiple myeloma. The '603 application's only specific disclosure is to the use of flurbiprofen to provide a chemoprotective effect from colon cancer. This is not a teaching or suggestion that the claimed compounds, etodolac, R-etodolac, and analogs thereof, would be useful for treating multiple myeloma. In addition, the Examiner has acknowledged that the cancers disclosed "include very divergent types of cancers" and that colorectal cancer is emphasized. Thus, one skilled in the art would not be expected to have a reasonable expectation of success, based on the disclosure of the '603 application, that the claimed compounds will be effective for treating multiple myeloma. There are many combinations that could be selected from the '603 application. The specific selection of the etodolac, or analogs thereof, for an effective treatment of multiple myeloma, is

not obvious in view of the '603 application disclosure, particularly in view of the numerous experiments that would be required.

When considered in its entirety, the disclosure of the '603 application would not motivate a person skilled in the art to use the specific group of compounds disclosed in the instant application as a cytotoxic agent, to reduce the viability of or to sensitize cancer cells. Thus, because the '603 application only discloses the use of the R-NSAID compounds to elicit a chemoprotective effect, the instant claims are not *prima facie* obvious over the disclosure of the '603 application, and withdrawal of this rejection is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6968 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 7th day of June, 2004.

PATRICIA A. HULTMAN
Name

Signature